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10/561,214	08/29/2006	Tomoyuki Hasegawa	Q92149	2252

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EXAMINER	
MOORE, SUSANNA	
ART UNIT	PAPER NUMBER
1624	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,214	HASEGAWA ET AL.	
	Examiner	Art Unit	
	SUSANNA MOORE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-15,20 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-15,20 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/25/09,2/25/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's arguments, see Remarks, filed 3/16/2009, with respect to Office Action mailed 11/25/2008 have been fully considered. Some of the rejections have been withdrawn, others have been maintained, and some are new rejections or are new as a result of Applicant's amendments. Thus, this is a Final Office Action. In summary, claims 1-9, 11-15, 20 and 24 are currently pending.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 3/25/2009 and 2/25/2009 was filed after the mailing date of the Nonfinal Office action on 11/25/2008. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. The DSs have the same references cited and thus only one was considered.

Specification

The objection of the title of the invention is **withdrawn** based on the amendments.

The objection of the abstract of the disclosure is **withdrawn** based on the amendments.

The disclosure is objected to because of the following informalities: a substitute specification is required pursuant to 37 CFR 1.125(a) because the instant specification is not grammatically correct. A substitute specification in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required. The substitute specification filed must be accompanied by a statement that it contains no new matter. The following is just one of the examples which

can be shown, "In the specification of WO 02/053565, "as a concrete compound, 8-(3-pentylamino)-2-methyl-3-(2-chloro-4methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine hydrochloride was described. A thermal stability of this compound was bad, and as for this compound, it separated and happened to the escape of the hydrochloric acid more than a certain temperature. Besides, crystalline of this compound was bad, and a yield of the crystal was very low." See page 5, first paragraph. Appropriate correction is required.

Claim Objections

The objection of claims 10-12, 17 and 20 because of the following informalities: the abbreviation/acronym, "CRF" should be spelled-out is **withdrawn** based on the amendments.

The objection of claims 10-15 because of the following informalities: claims 10-15 are substantial duplicate of claim 8 is **withdrawn** based on the amendments.

The objection of claim 17 because of the following informalities: claim 17 is a substantial duplicate of claim 8 is **withdrawn** based on the amendments.

The objection of claims 16, 18, 19, 22 and 23, drawn to an invention nonelected without traverse in the paper of 8/11/2008 is **withdrawn** based on the amendments.

Claims 1, 12 and 20 is objected to because of the following informalities: the term "Corticotropin Releasing Factor" should not be capitalized. Appropriate correction is required.

Claim 5 is objected to because of the following informalities: the claim is missing a period at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The rejection of claims 8-15 for being indefinite due the preamble of claim 8 which states "A pharmaceutical composition comprising the compound described in claim 1… " is **withdrawn** based on the amendments.

The rejection of claim 17 for being indefinite due to the preamble of claim 17 which states "A CRF antagonist comprising… "is **withdrawn** based on the amendments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 20 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "a disease resulting from elevated activity of Corticotropin Releasing Factor" is indefinite. There is no standard list of diseases which are from elevated activity of Corticotropin Releasing Factor. The passage spanning lines 14-18, page 12 and page 13, provides a list of unrelated conditions using open language "for example". What other diseases are contemplated? It is unclear what diseases and treatments Applicant is intending to encompass because there are so many different diseases.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim states, "which is superior in thermal stability," which is indefinite because it is not clear what Applicant is intending. The "superior in thermal stability" is determined relative to something else, e.g. a standard or control. Please provide guidance as to how the thermal stability is measured.

Claim 20 is vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by CRF antagonists. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one

dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in inflammation and neuropsychiatric disorders, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the

determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, anti-inflammatory agents and anti-neurodegenerative agents, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Applicant traverses the rejection by stating, "Therefore, Applicants submit that antagonizing the activity of CRF does not require undue experimentation because it does not require determining whether a given disease responds to the compound or not." This is not persuasive. It is not known what is meant by antagonizing the activity of CRF, i.e. the scope of the claims must be clear so that the public is informed of the boundaries of what constitutes infringement of the patent. The rejection of claim 20 is on the grounds that it is indefinite, in that it is not known which diseases are capable of being responsive to the antagonizing the activity of CRF. Why else would you antagonize the CRF receptor if not to treat a disease, which Applicant has cited on pages 12-13? The scope of diseases and/or disorders associated with the antagonizing the activity of CRF could alter over time. Thus, Applicant is not entitled to preempt the efforts of others.

Claims 11-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with

the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(A) Breadth of claims.

(a) Scope of the compounds. The instant claim 8-(3-pentylamino)-2-methyl-3-(2-chloro-4methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine methanesulfonate.

(b) Scope of the diseases covered. Claims 11-15 are drawn to a method of treating a disease resulting from elevated activity of corticotrophin releasing factor, which are those diseases listed on pages 12-13 of the Specification. Furthermore, the scope is not known since based on the 112 second paragraph rejection addressed above.

The disclosure includes neuropsychiatric disorders, digestive system diseases, respiratory diseases, endocrine diseases, metabolic diseases, circulatory system diseases, skin diseases,

urogenital diseases, eye diseases and musculoskeletal system diseases. Some of these will be elaborated further below.

Skin diseases are any diseases that affect the skin. The following includes a list of such diseases, but is not limiting to: acne, actinic keratosis, angioma, athlete's foot, aquagenic pruritus, atopic dermatitis, baldness, basal cell carcinoma, bed sore, Behcet's disease, blepharitis, boil, Bowen's disease, bullous pemphigoid, canker sore, carbuncles, cellulitis, chloracne, chronic dermatitis, cold sores, contact dermatitis, creeping eruption, dandruff, dermatitis, dermatitis herpetiformis, dermatofibroma, diaper rash, dyshidrosis, eczema, epidermolysis bullosa, erysipelas, erythroderma, Ferguson's Disease, friction blister, hidradenitis suppurativa, hyperhidrosis, ichthyosis, impetigo, jock itch, kaposi's sarcoma, keloid, keratoacanthoma, keratosis pilaris, lice infection, lichen planus, lichen simplex chronicus, lipoma, lymphadenitis, malignant melanoma, melasma, miliaria, molluscum contagiosum, nummular dermatitis, Paget's disease of the nipple, pediculosis, pemphigus, perioral dermatitis, photoallergy, photosensitivity, pityriasis rosea, pityriasis rubra pilaris, porphyria, psoriasis, Raynaud's disease, ring worm, rosacea, scabies, scleroderma, sebaceous cyst, seborrheic keratosis, seborrhoeic dermatitis, shingles, skin cancer, skin tags, spider veins, squamous cell carcinoma, stasis dermatitis, tick bite, tinea barbae, tinea capitis, tinea, corporis, tinea cruris, tinea pedis, tinea unguium, tinea versicolor, tinea, tungiasis, urticaria, vitiligo and warts.

Seizures are temporary abnormal electro-physiologic phenomena of the brain, resulting in abnormal synchronization of electrical neuronal activity. They can manifest as an alteration in

mental state, tonic or clonic movements, convulsions, and various other psychic symptoms. They are due to temporary abnormal electrical activity of a group of brain cells. The medical syndrome of recurrent, unprovoked seizures is termed epilepsy, but some seizures may occur in people who do not have epilepsy. Seizure is often associated with a sudden and involuntary contraction of a group of muscles. However, a seizure can also be as subtle as marching numbness of a part of body, a brief loss of memory, sparkling or flashes, sensing an unpleasant odor, a strange epigastric sensation or a sensation of fear. Therefore seizures are typically classified as motor, sensory, autonomic, emotional or cognitive. These include absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures.

Neuropyschiatric disorders covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; Gerstmann-Straussler-Scheinker Disease (GSS); Pick's Disease; Diffuse Lewy Body Disease; Hallervordon-Spatz disease; progressive progressive familiar myoclonic supranuclear palsy epilepsy; Corticodentatonigral (Steele-Richardson-Olszewski); degeneration; Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; ShyoDrager syndrome; Friedrich's ataxia and other spinocerebellar degenerations; olivopontocerebellar atrophy (OPCA); spasmotic torticollis; striatonigral degeneration; - various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary. lateral sclerosis; peroneal muscular atrophy (Charcot-Marie- Tooth); Creutzfeldt-Jakob

Disease (CJD); hypertrophic interstitial polyneuropathy (Dejerine-Sottas); retinitis pigmentosa; Leber's Disease; and Hypertrophic interstitial polyneuropathy. These exhibit a very broad range of effects and origins. For example, some give progressive dementia without other prominent neurological signs, Such as Alzheimer's disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some are abnormalities of posture, movement, or speech, such as striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's disease and FTDP- 17, and other such as Parkinson's clearly do not. Some affect only vision such as retinitis pigmentosa. Even within those that fall into the same category of effects, there are often striking differences. For example, Alzheimer's disease and Pick's disease both give progressive dementia without other prominent neurological signs. However, the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's disease. There are differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are different. Thus, FTDP-17 comes from chromosome 17, Huntington's disease from 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to 21.

Digestive system disorders can be defined as any disease or disorder associated with the GI tract, which include the mouth, esophagus, stomach, intestines, rectum and anus, as well as the spleen, bile ducts, gall bladder, liver and pancreas. As recited, the scope of the claim can include, but is not limited to, tooth decay, periodontal disease, abscesses, canker sores, cold sores, oral cancer, gastroesophageal reflux disease, dysphagia, esophagus cancer, circopharyngeal incoordination, achalasia, diverticula, burning mouth syndrome, pancreas cancer, Crohn's disease, colon polyps, diverticular disease, intestinal parasites, salivary gland disease, sialhorria, dentigerous cyst, glossitis, benign migratory, Ludwig's Angina, Melkerson-Rosenthal Syndrome, xerostamia, Pierre-Robin Syndrome, diabetes, lactose intolerance, bruxism,ulcerative colitis, cystic fibrosis, pernicious anemia, tropical sprue, cirrhosis, Bassen-Kornzweig syndrome, pancreatitis, Shwachman-Diamond syndrome, anal cancer, acute pancreatitis, anal fissure, anal fistula, colorectal cancer, hemorrhoids, perirectal abscess, proctitis, rectal prolapse, functional constipation, liver cancer, diarrhea, ankyloglossia, Irritable Bowel Syndrome, functional dyspepsia, peptic ulcer, intussusception, Coeliac disease, Whipple's disease, lymphoma, incontinence, chronic pancreatitis, Hirschsprung's disease, infant regurgitation, biliary disorder, hemochromatosis, Wilson disease, tyrosinemia, alpha 1 antitrypsin defiency, glycogen storage disease, primary sclerosing cholangitis, hepatitis A, hepatitis B, hepatitis C, Reyes's syndrome.

Eye disorders can be defined by the following diseases, but are not limited to: Hordeolum ("stye" or "sty"), Chalazion, Blepharitis, Entropion and trichiasis, Ectropion, Lagophthalmos, Blepharochalasis, Ptosis, Xanthelasma of eyelid, Dermatitis of eyelid due to Demodex species,

leishmaniasis, loiasis, onchocerciasis, phthiriasis, herpesviral (herpes simplex) infection, leprosy, molluscum contagiosum, tuberculosis, yaws, zoster, Involvement of eyelid in impetigo, Dacryoadenitis, Epiphora, Dysthyroid exophthalmos, Conjunctivitis, Pterygium, Subconjunctival hemorrhage, Scleritis, Keratitis, Corneal ulcer / Corneal abrasion, Snow blindness / Arc eye, Thygeson's superficial punctate keratopathy, Corneal neovascularization, Fuchs' dystrophy, Keratoconus, Keratoconjunctivitis sicca, Iritis, Uveitis, Cataract, Retinal detachment, Retinoschisis, Hypertensive retinopathy, Diabetic retinopathy, Retinopathy, Retinopathy of prematurity, Age-related macular degeneration, Macular degeneration, Retinitis pigmentosa, Macular edema,Glaucoma, Floaters, Leber's hereditary optic neuropathy, Strabismus, Ophthalmoparesis, Progressive external ophthalmoplegia, Esotropia, Exotropia, Hyperopia (Farsightedness), Myopia, (Nearsightedness), Astigmatism, Anisometropia, Presbyopia, Internal ophthalmoplegia, .Amblyopia (lazy eye), Leber's congenital amaurosis, Scotoma (blind spot), Color blindness, Achromatopsia / Maskun, Nyctalopia (Nightblindness), Blindness, River blindness, Red eye, Argyll Robertson pupil, Keratomycosis, Xerophthalmia and Aniridia.

Circulatory disorders are all diseases of the heart and circulatory system in the body. This includes, but is not limited to, diseases of the heart, blood, veins, lymphatic vessels and lymph nodes, arteries, arterioles and capillaries and cerebrovascular diseases.

Some circulatory disorders are, but not limited to: atherosclerosis, aneurysm, angina pectoris, atrial fibrillation, cardiomyopathy, congenital defects, congestive heart failure, coronary heart disease, heart attack (myocardial infarction), high blood pressure / hypertension, mitral valve prolapse, systolic murmur, diastolic murmur, continuous murmur, pericarditis, peripheral

vascular disease, rheumatic heart disease, functional peripheral vascular disease, organic peripheral vascular disease, myocarditis, Long QT syndrome, endocarditis, arrthymia, aortic dissections, aortic stenosis, pulmonary stenosis, bicuspid aortic valve, subaortic stenosis, coarctation of the aorta, atrial septal defect, Ebstein's anomaly, ventricular septal defect, tetralogy of Fallot, tricuspid atresia, transposition of the great arteries, hypoplastic left heart syndrome, patent ductus arteriosus, mitral valve prolapse, valvular stenosis, stable angina, unstable angina, variant angina, angioplasty, arteriosclerosis, deep vein thrombosis, heart transplantation, low blood pressure, phlebitis, Raynaud's Disease, Shy-Drager Syndrome, Syndrome X, stroke, cerebrovascular disease, carotid endarterectomy, Thoracic Outlet Syndrome, thrombophlebitis, transient ischemic attack, Wegener's Granulomatosis, idiopathic thrombocytopenic purpura, Von Willebrand Disease and sickle cell anemia.

Respiratory disease is any disease that affects the lungs. These include, but are not limited to: influenza, bacterial pneumonia, viral pneumonia, bronchopneumonia, acute bronchitis, acute bronchiolitis, chronic bronchitis, asthma, status asthmaticus, bronchiectasis, chronic obstructive pulmonary disease, Coalworker's pneumoconiosis, asbestos pneumoconiosis, dust pneumoconiosis, aluminosis, bauxite fibrosis, beryliosis, graphite fibrosis, siderosis, stannosis, tuberculosis, byssinosis, bagassosis, adult respiratory distress syndrome, pulmonary oedema, pulmonary eosinophilia, interstitial pulmonary disease with fibrosis, Hamman-Rich syndrome, idiopathic pulmonary fibrosis, abscess of lung and mediastinum, abscess of lung with pneumonia, pyothorax, empyema, pleural effusion, pleural plaque, pneumothorax, pulmonary collapse, interstitial emphysema, compensatory emphysema, diffuse alveolar hemorrhage

syndrome, pulmonary-renal syndrome, silicosis, lymphangioleimyomaosis, lymphoid interstitial pneumonia, pulmonary alveolar proteinosis, pulmonary langerhans' cell granulomatosis, pneumothorax, pneumomediastinum, pulmonary embolism, hepatopulmonary syndrome, portopulmonary hypertension and lung cancer.

These are just some of the diseases embraced by the scope of claims 11-15.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: The provided in the Specification on page 43 is very limited. The dosage range information on page 43 gives 10-20 mg of active compound, which is generic, the same for the many disorders covered by the Specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for any and all diseases encompassed by the scope of claims 11-15.

(D) State of the Prior Art: The is 8-(3-pentylamino)-2-methyl-3-(2-chloro-4methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine methanesulfonate. So far as the examiner is aware, no 8-(3-pentylamino)-2-methyl-3-(2-chloro-4methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine of any kind have been used for the treatment of any

and all the diseases encompassed by the scope of claims 11-15.

(E) Working Examples: The invention is drawn to the therapy of all the diseases listed under the Scope of diseases. There is one binding assay for the CRF1 receptor. There are no working examples or data in the Specification drawn to this utility to support the use of 8-(3-pentylamino)-2-methyl-3-(2-chloro-4methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine methanesulfonate to treat any or all the diseases covered by the Scope of diseases.

(F) Skill of those in the art: These diseases and disorders cannot be treated generally by any one drug. These are all different diseases and disorders, which occur at different locations and by different modes of action in the body. Hirschsprung's disease, one of the many mentioned above, is a disorder, which is primarily treated with surgery. The instant compound, 8-(3-pentylamino)-2-methyl-3-(2-chloro-4methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine methanesulfonate,is recited as useful in treating any or all functional gastrointestinal disorders, for which applicants provide no competent evidence. Coeliac disease is untreatable. Hepatitis is treatable with antiviral agents, a property these compounds not disclosed to have.

Obesity, a condition which is just the opposite of bulimia, is not treated with the same pharmacotherapy as weight loss. They are at opposite ends of eating disorders.

To date, there are no CRF1 antagonists used to treat Parkinson's disease patients or dyskinesias. Note that Parkinson's disease itself is not treatable, current therapies are directed only to symptom alleviation.

Note that many of the diseases listed in the Scope of diseases are "umbrella" terms that are very broad in scope. Such as dementia, most forms are untreatable. All forms of seizures are covered by the Scope, even those seizures that have nothing to do with the CRF1 receptors.

The great majority of these neurophyschiatric disorders have no treatment at all, and of those that do, none have been treated with such CFR1 antagonists as are disclosed here. The great diversity of diseases falling within the "neuropsychiatric disorder" category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer's disease has produced are means of providing acetylcholinesterase inhibition, unrelated to the mechanism of action in this case. Thus, the scope of claims is huge.

Acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon®, and Reminyl®), or voltage-dependent NMDA-antagonists (Memantine), properties these compounds are not disclosed to have. Indeed, CRF1 is not currently even considered an important research area, and thus the skill level in the art of CRF1 treatment for Alzheimer's Disease is especially low. The Palmer TRENDS in Pharmacological Sciences 23(9) 426-433 September 2002 article on drug therapy for Alzheimer's Disease is likewise mentioned; it too makes no mention of CRF1.

One of ordinary skill in the art knows that no organic cause has ever been found for IBS. There are at present no pharmaceutical treatments for IBS itself, just general medicines such as laxatives or tranquilizers for relief of symptoms. The reference Jones et al, "British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome." Gut 2000, (Suppl II)47:ii1-ii19) makes it clear that no pharmaceutical agent has been established as effective against this serious disorder.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder, which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

These are just a few of the diseases covered by the scope.

(G) The quantity of experimentation needed: Owing especially to the factors of A, C, E and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11-15, 20 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakai et. al. (WO 2002/053565, US equivalent 7034153 B2).

The instant Application is claiming 8-(3-Pentylamino)-2-methyl-3-(2-chloro-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine methanesulfonate,

simple compositions, a method of making the methanesulfonate salt and a method of antagonizing the CRF receptor with said salt.

Nakai et. al. is claiming 8-(3-Pentylamino)-2-methyl-3-(2-chloro-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine and pharmaceuticall acceptable salts thereof, see claim 1, column 253. The methansulfonate salt is taught in column 22, line 9. Nakai also teaches the intended use, see column 2, line 7. It is routine experimentation to make a methansulfonate salt of an amine compound. Furthermore, if the compound is obvious the method of making said compound is obvious. The fact that the crystalline property is being claimed of 8-(3-Pentylamino)-2-methyl-3-(2-chloro-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine methanesulfonate, simple compositions, a method of making the methanesulfonate salt does not overcome the obviousness between the reference and the instant Application. If the crystalline form of any compound is introduced into a pharmaceutically acceptable carrier, which is a liquid, the crystallinity of the compound is lost. Thus, said claims are rendered obvious by Nakai et. al.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the

application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Applicant traverses the above rejection by stating, "As described in the instant specification (page 5, lines 1-11), Applicants note that there are potential problems, e.g., inferior stability, low yield, associated with 8-(3-Pentylamino)-2- methyl-3-(2-chloro-4-methoxyphenyl)-6,7-dihydro-5H cyclopenta[d]pyrazolo[1,5-a]pyrimidine hydrochloride. On the other hand, the claimed compound (i.e., methanesulfonate salt form) exhibits unexpectedly superior thermal stability over the hydrochloride salt form (page 11, lines 10-25). Additionally, Applicants also note that the effect is specific to the methanesulfonate salt because the thermal stability cannot be obtained by other pharmaceutically acceptable salts. For example, phosphoric acid salt of 8-(3-Pentylamino)-2-methyl-3-(2-chloro'4-methoxyphenyl)- 6,7.dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine has endothermic and exothermic peaks and has a problem in thermal stability. In this respect, it is surprising that one salt form can provide such a big effect on thermal stability. In view of foregoing, Applicants submit that the present invention is not obvious over Nakai et al."

This is not found persuasive. These results are not unexpected. It is known in the art that mesylate salts produce higher melting point compounds, see Bastin et. al. (Organic Process & Development, 2000, 4, pages 427-435). On page 431, the RPR 127963 compound was produced in five crystalline salts, i.e. hydrochloride, mesylate, citrate, tartrate and sulfate, see first full

paragraph in the left-hand column. Also note in the right-hand column, first full paragraph where the mesylate and sulfate salts of said compound are described as having high melting points. Moreover, the mesylate salt is one of the most popular anionic salts which is FDA approved commercially, see Berge et. al. (Journal of Pharmaceutical Sciences, 1977, pages 1-19), see page 2, Table 1, right hand side. One of ordinary skill in the art would make the mesylate salt based on the Berge reference and expect a higher melting point compound, based on the Bastin reference. Thus, the rejection is **maintained**.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9, 11-15, 20 and 24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 7034153. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the reasons provided in the 103 rejection listed above.

Applicant traverses the above rejection by stating, "The present invention is distinct and non-obvious over US Patent No. 7,034,153 (Nakai et al.) for the reasons set forth in Applicants' arguments above, in response to the103(a) rejection, arguments herein incorporate by reference and applied." This is not found persuasive for the reasons set forth above in the 103 rejection. Thus, the rejection is **maintained**.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSANNA MOORE whose telephone number is (571)272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susanna Moore/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624